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Anemia After Orchiectomy

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The decrease in testosterone production associated with bilateral orchiectomy may result in normocytic anemia in men. We sought to determine the effect of orchiectomy on hemoglobin concentration. Patients were evaluated at the Mayo Clinic in 1993 and 1994 and underwent bilateral orchiectomy for prostate carcinoma. All patients were seen by one of the staff urologists. Patients were included if they had a normal preoperative complete blood cell count and serum levels of creatinine, if they remained without disease progression (suppressed prostate-specific antigen level and no evidence of clinical progression on review), and if they had normal serum levels of creatinine and mean corpuscular volume during the follow-up period. The patients could have no other cause of anemia. The complete blood cell count, prostate-specific antigen level, and serum level of creatinine were determined preoperatively and at least once (>90 days) after orchiectomy. Sixty-four patients were included in the analysis (median age, 68 years). The median decrease in hemoglobin concentration was 1.2 g/dL after orchiectomy. There was a statistically significant difference in the hemoglobin concentration before orchiectomy compared with postoperative values at all the intervals studied, both by the paired group t-test and the Kruskal-Wallis test. There is a clinically and statistically significant decrease in hemoglobin concentration after orchiectomy. Knowledge of this phenomenon may prevent unnecessary diagnostic work-up in men with normocytic anemia after bilateral orchiectomy. Am. J. Hematol. 59:230–233, 1998. © 1998 Wiley-Liss, Inc.

Key words: androgens; anemia; erythropoiesis; hemoglobin; orchiectomy; prostate cancer

INTRODUCTION

Androgens have burst-promoting activity in erythropoiesis [1,2], and their physiologic effect in erythrocyte production is suggested by the anemia associated with hypogonadism. Bilateral orchiectomy is a major therapeutic option in the management of metastatic prostate cancer [3]. An objective response is achieved in up to 59% of patients after orchiectomy [4]. Bilateral orchiectomy results in a marked decrease in the circulating levels of androgens. In our clinical practice, we have observed that mild anemia develops in patients after orchiectomy for prostate cancer. We hypothesize that the marked androgen deprivation associated with bilateral orchiectomy may lead to a decreased concentration of hemoglobin. Although the effects of androgen administration on hematopoiesis have been studied extensively, the clinical significance for patients undergoing orchiectomy has not been studied systematically. Herein, we describe the occurrence of normocytic anemia after bilateral orchiectomy that is not explained by other factors.

MATERIALS AND METHODS

A computerized search was conducted of the medical records of all men who had bilateral orchiectomy at the Mayo Clinic in 1993 and 1994. The inclusion criteria for the study were: 1. bilateral orchiectomy for prostate cancer; 2. normal preoperative complete blood cell count (including mean corpuscular volume); 3. normal preoperative serum level of creatinine; 4. adequate follow-up data for more than 90 days after orchiectomy, including determination of at least one complete blood cell count, serum level of creatinine, and prostate-specific antigen; 5. normal serum level of creatinine and normal mean corpuscular volume throughout the follow-up period; 6. complete response to orchiectomy with no evidence of disease progression, as based on review of medical rec-

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ords and suppressed level of prostate-specific antigen; and 7. no other explanation for anemia.

The postoperative laboratory values were grouped into four intervals: group 1, 90 to 180 days after orchiectomy (n = 31); group 2, 181 to 360 days (n = 42); group 3, 361 to 720 days (n = 38); and group 4, more than 720 days (n = 11). (Some measurements in different groups were from the same patient.) Group 0 consisted of the preoperative (baseline) laboratory values of all patients. Although the blood loss in orchiectomy usually is minimal, we excluded any laboratory value obtained less than 90 days after orchiectomy. Preoperative hemoglobin values (group 0) were compared with the postoperative values obtained at each of the four intervals (groups 1 to 4).

Statistical analysis included simple descriptive statistics of the preoperative and postoperative values of hemoglobin, mean corpuscular volume, creatinine, and prostate-specific antigen. A nonparametric test (Kruskal-Wallis) was used to test the change in hemoglobin concentration after orchiectomy. Simple linear regression analysis was used to assess for any trend in hemoglobin concentration for preoperative and postoperative values combined and for postoperative values alone. A paired t-test was used to assess the change in hemoglobin concentration before and after orchiectomy (null hypothesis, change = 0). All calculations were two-sided and an α level of significance of 0.05 was determined. The Bonferroni correction was made to test significance between the different comparisons (0.05/number of observations, corrected). Statistical analysis was performed with Stat View, version 4.02 for Macintosh (Abacus Concepts Inc., Berkeley, CA).

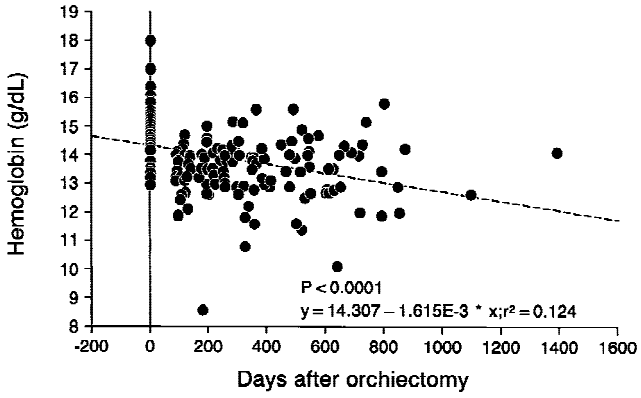

Fig. 1. Linear regression analysis for preoperative and postoperative hemoglobin values.

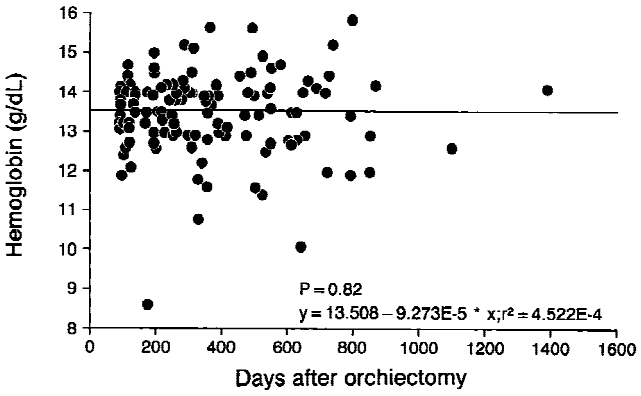

Fig. 2. Linear regression analysis for postoperative hemoglobin values.

RESULTS

Of the 187 patients with adequate follow-up information, 123 were excluded because of potentially confounding factors: 14 for an abnormal baseline complete blood cell count; 72 for abnormal serum levels of creatinine before or after orchiectomy; 29 for progression of prostate cancer after orchiectomy; and eight for other causes of anemia. Thus, 64 patients, with a median age of 68 years, were included in the analysis. Median preoperative values were as follows: hemoglobin concentration, 14.8 g/dL; creatinine, 1.09 mg/dL (range, 0.9 to 1.2 mg/dL); mean corpuscular volume, 89.6 fL (range, 81.9 to 99.3 fL); and prostate-specific antigen, 22.19 ng/ml (range, 0.2 to 197 ng/ml).

On linear regression analysis, a trend was noted for decreasing hemoglobin concentration (ANOVA, F 26.12, $P < 0.0001$) (Fig. 1). On linear regression of the postoperative values, no trend could be detected (Fig. 2).

The preoperative mean hemoglobin concentration (n = 64, group 0) was compared with the postoperative values at 90 to 180 days (n = 32, group 1), 181 to 360 days (n = 42, group 2), 361 to 720 days (n = 38, group 3), and >720 days (n = 11, group 4) (Table I). The difference between the hemoglobin concentration preoperatively (group 0) and each of the postoperative intervals studied (groups 1 to 4) was statistically significant by the paired group t-test (Table II). There was no difference between the four postoperative groups. The Kruskal-Wallis test was highly significant for a difference between groups ($P < 0.0001$). In 37 patients (58%) the hemoglobin fell to a value below the lower limit of normal at some point after the orchiectomy.

DISCUSSION

There is a clinically and statistically significant decrease in hemoglobin concentration after orchiectomy. Although our observations do not provide a pathophysiologic explanation for this, we propose that it is a result of androgen deprivation. The use of androgenic steroids in aplastic anemia [5], breast cancer, renal failure [6], and athletes has been associated with an increase in hemoglobin concentration. Our hypothesis is that a decrease in

TABLE I. Comparison of Hemoglobin Concentration Preoperatively and at Various Times Postoperatively*

Group	No. of patients	Mean hemoglobin, g/dL	Standard deviation	Median	Range, g/dL
0, preop	64	14.8	0.98	14.8	13–18
1, 90–180 days postop	32	13.4	1.13	13.7	8.6–14.7
2, 181–360 days postop	42	13.6	0.98	13.7	10.8–15.6
3, 361–720 days postop	38	13.5	1.03	13.6	10.1–15.6
4, >720 days postop	11	13.5	1.35	13.4	11.9–15.8

*Preop, preoperative; postop, postoperatively. The median decrease in hemoglobin concentration after orchiectomy was 1.2 g/dL. At a median follow-up time of 350 days, 78% of men had a decrease in hemoglobin concentration of at least 1 g/dL and 29% had a decrease of 2 g/dL or greater. The median duration at which the maximal decrease in hemoglobin concentration occurred was 349 days.

TABLE II. Comparison of Hemoglobin Concentration Preoperatively by Postoperative Group*

Comparison groups[a]	Mean difference in hemoglobin, g/dL	95% CI	*t* value	*P* value	Range
Group 0 vs. group 1	1.45	0.96–1.94	6.01	<0.0001	−1.0–6.9
Group 0 vs. group 2	1.23	0.97–1.48	9.78	<0.0001	−0.5–2.9
Group 0 vs group 3	1.35	0.98–1.72	7.42	<0.0001	−0.4–4.0
Group 0 vs. group 4	1.18	0.48–1.75	3.92	0.0029	−0.6–3.0

*CI, confidence interval.
[a]Definition of groups: group 0, preoperative; group 1, 90–180 days postoperatively; group 2, 181–360 days postoperatively; group 3, 361–720 days postoperatively; group 4, >720 days postoperatively.

hemoglobin concentration follows the marked androgen deprivation that occurs after bilateral orchiectomy. From our observations, it is clear that the hemoglobin concentration tends to decrease by one to two g/dL after orchiectomy. This results in hemoglobin concentrations that frequently occur within the normal range for females.

Potential confounding factors include bone marrow involvement by prostate cancer and anemia of chronic disease. To limit these confounders, we ensured that all patients included in the study were free from disease progression. The peripheral blood smear was not suggestive of a bone marrow-replacing process that would result in a leukoerythroblastic peripheral blood smear. In fact, except for normocytic anemia, the complete blood cell count was normal in all the patients. Clinical and experimental data in humans and other animals have documented a similar phenomenon [7–14]. The anemia in these animals resolved with the exogenous administration of androgens. Bilateral orchiectomy is used exclusively in the treatment of men with advanced prostate cancer. In these patients, there is some residual androgenic hormone production by the adrenals [15,16]. Whether complete androgenic blockade would induce a more profound decrease in hemoglobin concentration is not known. Analysis of hematologic variables in patients undergoing androgenic blockade with gonadotropin analogues likely would yield the same results.

Work done by Weber and colleagues [17] has previously shown that reversible androgen deprivation in men leads to lowering of the hemoglobin levels within the normal range. They studied seven men treated with luteinizing hormone-releasing hormone (LH-RH) agonists. The testosterone levels fell to the castrate level in all patients and they had an associated drop in the hemoglobin of approximately one g. Interestingly, there was no associated increase in the serum erythropoietin level. This thus suggests that the anemia observed after orchiectomy could likewise be related to the resulting hypoandrogenic state.

In summary, we conclude that the lack of androgens after orchiectomy is associated with a significant decrease in hemoglobin concentration. The anemia is mild and does not need treatment. Knowledge of this phenomenon may prevent needless diagnostic evaluation of anemia after orchiectomy.

REFERENCES

1. Singer JW, Samuels AI, Adamson JW: Steroids and hematopoiesis. I. The effect of steroids on in vitro erythroid colony growth: Structure/activity relationships. J Cell Physiol 88:127, 1976.
2. Modder B, Foley JE, Fisher JW: The in vitro and in vivo effects of testosterone and steroid metabolites on erythroid colony forming cells (CFU-E). J Pharmacol Exp Ther 207:1004, 1978.
3. Huggins C, Stevens RE, Jr, Hodges CV: Studies on prostatic cancer: Effects of castration on advanced carcinoma of prostate gland. Arch Surg 43:209, 1941.
4. Robson M, Dawson N: How is androgen-dependent metastatic prostate cancer best treated? Hematol Oncol Clin N Am 10:727, 1996.
5. Locasciulli A, Porta F, Vossen JM, Bacigalupo A: Treatment of acquired severe aplastic anaemia (SAA) in children: An analysis of the EBMT-SAA working party (abstract). Bone Marrow Transplant (Suppl 2) 4:90, 1989.
6. Dainiak N: The role of androgens in the treatment of anemia of chronic renal failure. Semin Nephrol 5:147, 1985.
7. Crafts RC: Effects of hypophysectomy, castration, and testosterone propionate on hemopoiesis in adult male rat. Endocrinology 39:401, 1946.
8. van Dyke DC, Contopoulos AN, Williams BS, Simpson ME, Lawrence JH, Evans HM: Hormonal factors influencing erythropoiesis. Acta Haematol 11:203, 1954.
9. Finkelstein G, Gordon AS, Charipper HA: Effect of sex hormones on anemia induced by hemorrhage in rat. Endocrinology 35:267, 1944.
10. Sanchez-Medal L: The hemopoietic action of androstanes. Prog Hematol 7:111, 1971.
11. Garn SM, Ryan AS, Owen GM, Abraham S: Income matched black-

white hemoglobin differences after correction for low transferrin saturations. Am J Clin Nutr 34:1645, 1981.
12. Ammus SS: The role of androgens in the treatment of hematologic disorders. Adv Intern Med 34:191, 1989.
13. McCullagh EP, Jones R: Effects of androgens on blood count of men. J Endocrinol Metab 2:243, 1942.
14. Hamilton JB: Role of testicular secretions as indicated by effects of castration in man and by studies of pathological conditions and short lifespan associated with maleness. Recent Prog Horm Res 3:257, 1948.
15. Geller J, Albert J, Vik A: Advantages of total androgen blockade in the treatment of advanced prostate cancer. Semin Oncol (Suppl 1) 15:53, 1988.
16. Harper ME, Pike A, Peeling WB, Griffiths K: Steroids of adrenal origin metabolized by human prostatic tissue both in vivo and in vitro. J Endocrinol 60:117, 1974.
17. Weber JP, Walsh PC, Peters CA, Spivak JL: Effect of reversible androgen deprivation on hemoglobin and serum immunoreactive erythropoietin in men. Am J Hematol 36:190, 1991.